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Original Research

Phase II randomised discontinuation trial of cabozantinib in patients with advanced solid tumours

Patrick Schöffski [a,*], Michael Gordon [b], David C. Smith [c], Razelle Kurzrock [d], Adil Daud [e], Nicholas J. Vogelzang [f], Yihua Lee [g], Christian Scheffold [g], Geoffrey I. Shapiro [h]

[a] *Department of General Medical Oncology, Leuven Cancer Institute, University Hospital Leuven, Leuven, Belgium*
[b] *Pinnacle Oncology Hematology, Scottsdale, AZ, USA*
[c] *Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI, USA*
[d] *Moores Cancer Center, University of California, San Diego, San Diego, CA, USA*
[e] *Medical Center at Parnassus, University of California, San Francisco, San Francisco, CA, USA*
[f] *Comprehensive Cancer Centers of Nevada, US Oncology Research, Las Vegas, NV, USA*
[g] *Exelixis, Inc., South San Francisco, CA, USA*
[h] *Early Drug Development Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*

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KEYWORDS
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Abstract ***Background:*** Cabozantinib is an inhibitor of tyrosine kinases, including MET, vascular endothelial growth factor receptor, AXL and RET. This multi-cohort phase II randomised discontinuation trial explored anticancer activity of cabozantinib in nine tumour types.

Patients and methods: Cabozantinib was administered (100 mg, once daily) to patients with advanced, recurrent or metastatic cancers. Those with stable disease at week 12 were randomised 1:1 to cabozantinib or placebo. Primary end-points were objective response rate (ORR) at week 12 and progression-free survival (PFS) in the randomised phase.

Results: A total of 526 patients were enrolled. The highest ORR was observed in ovarian cancer (OC) (21.7%); the largest PFS benefit was observed in castration-resistant prostate cancer (CRPC) (median 5.5 versus 1.4 months for placebo; hazard ratio 0.14, 95% confidence interval: 0.04, 0.52). Disease control rates were >40% for CRPC, OC, melanoma, metastatic breast cancer (MBC), hepatocellular carcinoma (HCC) and non–small cell lung cancer. Median duration of response ranged from 3.3 (MBC) to 11.2 months (OC). Encouraging efficacy

* *Corresponding author*: Department of General Medical Oncology, Leuven Cancer Institute, University Hospitals Leuven, Faculty of Medicine, Department of Oncology, Laboratory of Experimental Oncology, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. Fax: +32 16 346901.
E-mail addresses: patrick.schoffski@uzleuven.be (P. Schöffski), mgordon@azpoh.com (M. Gordon), dcsmith@med.umich.edu (D.C. Smith), rkurzrock@ucsd.edu (R. Kurzrock), Adil.Daud@ucsf.edu (A. Daud), Nicholas.Vogelzang@usoncology.com (N.J. Vogelzang), ewalee@yahoo.com (Y. Lee), cscheffo@exelixis.com (C. Scheffold), geoffrey_shapiro@dfci.harvard.edu (G.I. Shapiro).

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results and symptomatic improvements prompted early suspension of the randomised stage and conversion to open-label non-randomised expansion cohorts. Dose reductions to manage adverse events (AEs) occurred in 48.7% of patients. The most frequent grade III–IV AEs were fatigue (12.4%), diarrhoea (10.5%), hypertension (10.5%) and palmar-plantar erythrodysesthesia syndrome (8.7%).

Conclusions: Clinical antitumour activity of cabozantinib was observed in a subset of tumour types: CRPC and OC were evaluated further in expansion cohorts. Phase III programs were initiated in CRPC and HCC. Interpretation of efficacy outcomes was limited by early termination of the randomised portion of the trial.

Trial registration number: NCT00940225.

1. Introduction

Cabozantinib, a small-molecule tyrosine kinase inhibitor (TKI), inhibits multiple receptor tyrosine kinases that are important in cancer pathobiology, including MET, the three vascular endothelial growth factor receptors (VEGFRs), AXL and RET. In preclinical studies, cabozantinib treatment was shown to inhibit tumour angiogenesis, invasiveness, metastasis and tumour progression [1–3]. In xenograft models, the primary effect of cabozantinib was the inhibition of tumour growth rather than volumetric shrinkage, suggesting that the primary clinical benefit of cabozantinib may be disease stabilisation. Therefore, classical oncology paradigms for phase II clinical evaluation (e.g. single-arm, non-controlled studies using objective response rate [ORR] as the primary end-point) might not adequately demonstrate the antitumour activity of cabozantinib.

Tumour stabilisation is best measured through the use of a controlled study, which ensures that differences detected between experimental and control arms are due to cytostatic activity and not the inherent indolent nature of a tumour [4,5]. In settings without an appropriate active control, a randomised discontinuation trial (RDT) attempts to assess cytostatic effect while limiting placebo exposure [6–8]. In RDTs, patients achieving tumour stabilisation while receiving experimental treatment during an initial lead-in period are identified as potentially experiencing cytostatic benefit. At a predefined time point, these patients are randomised to either continue experimental treatment or to receive placebo. Through this process, heterogeneity to drug response is decreased within the randomised population compared with studies carrying out randomisation at initiation.

The objective of the present multi-cohort phase II RDT was to evaluate the clinical anticancer activity of cabozantinib for multiple solid-tumour types. The trial used an adaptive design, whereby a study oversight committee reviewed ongoing efficacy and safety data and made recommendations for cohort enrolment and study conduct.

2. Patients and methods

2.1. Patients

This phase II RDT evaluated the antitumour activity of cabozantinib in nine solid-tumour types, which defined individual cohorts (ClinialTrials.gov, NCT00940225). The RDT design consisted of a 12-week lead-in stage with open-label treatment of cabozantinib followed by a placebo-controlled randomised stage for patients who achieved stable disease (SD) during the lead-in stage (Fig. 1). The study protocol was approved by all local/institutional review boards for human investigations as appropriate, and all patients provided written informed consent. Eligible patients had pathologically confirmed malignant solid tumours in an advanced, recurrent or metastatic stage with measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 [9]. Patients were enrolled in the following tumour cohorts: castration-resistant prostate cancer (CRPC), melanoma (MEL), ovarian cancer (OC; epithelial ovarian cancer, primary peritoneal or fallopian tube carcinoma), non–small cell lung cancer (NSCLC), metastatic breast cancer (MBC), hepatocellular carcinoma (HCC), gastric/gastroesophageal junction adenocarcinoma (GC), small-cell lung cancer (SCLC) and pancreatic adenocarcinoma (PAC). Additional eligibility criteria for the tumour cohorts are included in the Supplementary Information-Tumour-specific cohort eligibility.

2.2. Study drug administration

During the 12-week lead-in stage, patients received 100-mg daily doses of cabozantinib capsules. After this lead-in stage, study sites randomised patients via an interactive web response system, which provided a blinded study drug package identifier. Cabozantinib and placebo were colour-, size- and shape-matched; patients and study site personnel were blinded to treatment assignment. The randomisation schedule was stratified by

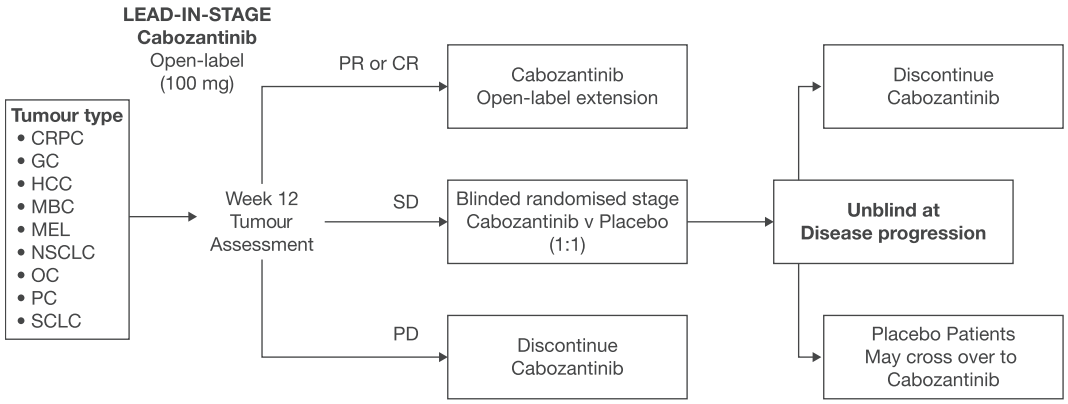

Fig. 1. **Multi-cohort randomised discontinuation trial design**. CR, complete response; CRPC, castration-resistant prostate cancer; GC, gastric/gastroesophageal junction adenocarcinoma; HCC, hepatocellular carcinoma; MBC, metastatic breast cancer; MEL, melanoma; NSCLC, non–small cell lung cancer; OC, ovarian cancer; PAC, pancreatic adenocarcinoma; PD, progressive disease; PR, partial response; SCLC, small-cell lung cancer; SD, stable disease.

tumour type and within each tumour type permuted blocks were used to maintain the 1:1 ratio between cabozantinib and placebo arms.

Protocol-defined dose modifications, including interruptions (up to 3 weeks) and dose reductions, were used to manage adverse events (AEs). Treatment could be reduced at the discretion of the investigator to 60 mg, 40 mg and then 20 mg. Patients could continue treatment until disease progression or unacceptable toxicity. Study treatment in the randomised stage was administered in a double-blind fashion.

2.3. Study assessments

The primary end-point of the lead-in phase was ORR at week 12, and the primary end-point of the randomised phase was PFS. Additional end-points included the disease control rate (DCR) at week 12, duration of response (DOR) and PFS from first dose of cabozantinib in all patients. Tumour assessments by computed tomography or magnetic resonance imaging were performed at screening and every 6 weeks after the first dose of study treatment. Tumour response and progression were determined by the investigator using RECIST 1.0. Imaging continued until permanent discontinuation of study treatment due to documented progressive disease (PD) or initiation of subsequent anticancer therapy. Changes in tumour markers were not considered for determination of progression. Although study treatment could be discontinued upon clinical deterioration, every effort was made to document radiographic progression.

Safety was evaluated by assessment of AEs, vital signs, electrocardiograms and standard laboratory tests. Seriousness of AEs, severity grade per Common Terminology Criteria for Adverse Events, version 3.0, and relationship to study treatment were assessed by the investigator.

2.4. Statistical considerations

The study used an adaptive design with an assumed SD rate of 35% at week 12 to estimate the target enrolment from the number of patients planned for randomisation (Supplementary Fig. S1). The target enrolment of 200 patients per cohort was chosen to achieve the goal of 70 randomised patients and 52 events post randomisation. The design had an 80% power to detect a hazard ratio (HR) of 0.5 for progression-free survival (PFS) between cabozantinib and placebo with a two-sided alpha of 0.1. Under this design, the minimum observed effect that would demonstrate statistical significance for PFS was a 58.7% improvement (HR = 0.63). Given that this was a phase II trial intended to generate hypotheses for further study, there was no adjustment for multiple comparisons. Up to an additional 300 patients could be enrolled in cohorts deemed not suitable for full accrual to the randomised stage. The study oversight committee was responsible for prioritisation of tumour cohorts based on continuous review of emerging efficacy and safety data. Stopping rules were based on conditional probability to project futility (e.g. enrolment was suspended in tumour cohorts deemed unlikely to benefit from cabozantinib or if the ORR after the 12-week lead-in stage was higher than anticipated such that the randomised stage was unwarranted).

ORR was defined as the proportion of patients with a best overall response of confirmed complete response (CR) or partial response (PR) during the lead-in stage. PFS in the randomised stage was defined as the time from randomisation until the earlier of radiographic progression or death. The comparison of PFS between the cabozantinib and placebo arms was performed using the log-rank test in the randomised population. The median duration of PFS and the associated 95% confidence interval (CI) for each treatment arm were estimated using the Kaplan–Meier method. The HR was

estimated using a Cox regression model with treatment as the only covariate.

DOR was summarised for patients treated in the lead-in and/or randomised stage and was defined as the time from the tumour assessment of the first documented PR or CR that was subsequently confirmed at least 28 d later until the date of disease progression. Median DOR and the associated 95% CI were estimated using the Kaplan–Meier method. DCR was defined as the proportion of patients treated in the lead-in stage with a best overall response of CR, PR or SD at Week 12.

PFS from first dose of cabozantinib in all patients was estimated using a piecewise method. For this analysis, all patients contributed to the PFS estimate for the first 12 weeks of therapy. PFS after week 12 was estimated using a weighted average of group-specific PFS from the two groups continuously treated with cabozantinib: 1) continued open label and 2) randomised to cabozantinib. When combining the group-specific PFS estimates, the weights were the proportion of the sample size of patients in the group of continued open label versus patients in the randomised population [6].

3. Results

3.1. Patients and treatment

Between September 2, 2009 and July 19, 2011, 795 patients were screened for eligibility, and 526 patients were enrolled in nine tumour-specific cohorts at 42 sites in the United States, Belgium, Israel and Taiwan. Baseline characteristics and cohort distribution are summarised in Supplementary Table S1, and a breakdown of metastatic areas can be found in Supplementary Table S2. Among 526 patients who received ≥1 dose of study treatment, 233 (44.3%) discontinued before completing the 12-week lead-in stage, 135 (25.7%) underwent randomisation at the end of week 12 and 158 (30.0%) continued cabozantinib in the open-label extension without being randomised, either because they experienced PR or CR during the lead-in stage or because randomisation was discontinued before they reached week 12. Among 135 randomised patients, 67 were randomly assigned to receive cabozantinib and 68 to placebo. Of patients randomised to placebo, 53 crossed over to receive open-label cabozantinib, either after progression on placebo or when the study was unblinded, and 15 discontinued without crossing over (Supplementary Fig. S2). Median duration of exposure to cabozantinib was 86 d (range: 4–1232 d), and median average daily dose was 69.8 mg (range: 15.4–100 mg). The most common reasons for treatment discontinuation in the study were radiographic progression (54.4%), AEs (20.3%) and clinical deterioration (10.1%).

3.2. Tumour response during the lead-in stage per investigator

An ORR ≥10% was observed in three tumour cohorts: OC, 21.7% (15/70); MBC, 13.6% (6/45) and NSCLC, 10% (6/60) (Table 1). One confirmed CR was observed in the OC cohort. A reduction in the sum of target lesion size was observed in 301 of 526 (57.2%) patients across all tumour types (Fig. 2). DCRs at week 12 ≥ 40% were observed for HCC, CRPC, OC, MBC, SCLC and MEL. Low rates (≤15%) of PD as best response were observed in HCC, CRPC and OC.

3.3. Progression-free survival

Assessment of PFS during the randomised stage indicated improvements in disease control with cabozantinib compared with placebo in CRPC (median PFS, 5.5 versus 1.4 months; HR = 0.14, 95% CI: 0.04, 0.52), MEL (4.5 versus 2.8 months; HR = 0.47, 95% CI: 0.16, 1.35) and HCC (2.5 versus 1.4 months; HR = 0.82, 95% CI: 0.31, 0.12) (Table 1, Supplementary Fig. S3). Characterisation of PFS during the randomisation stage for the other tumour cohorts was not possible, given the low number of events.

In the evaluation of PFS from the first dose of cabozantinib in all patients, the highest median PFS results were observed in the CRPC (6.8 months), OC (5.5 months), HCC (5.2 months), MBC (4.3 months) and NSCLC (4.0 months) cohorts.

3.4. Safety

AEs, irrespective of causality, occurred in 99.6% of patients with 392 (74.5%) experiencing at least one grade ≥III AE (Table 2). The most common grade ≥III AEs were fatigue, 65 (12.4%); diarrhoea, 55 (10.5%); hypertension, 55 (10.5%) and palmar-plantar erythrodysesthesia syndrome, 46 (8.7%). Overall, 390 patients (74.1%) had AEs leading to dose reduction or interruption. Dose reductions across all tumour cohorts occurred in 256 (48.7%) patients, with 85 (16.2%) having two dose reductions and 20 (3.8%) having three dose reductions. Median time to first dose reduction was 47.5 d (range, 11–470). Deaths occurring through 30 d after the last dose of cabozantinib were mainly related to disease progression. Eleven patients (2.1%) continuously treated with cabozantinib expired because of causes other than disease progression (1 patient each died of acute peritonitis, bilateral pneumonia, enterocutaneous fistula, gastrointestinal bleeding, haemorrhage, perforated bowel, pneumonia, possible respiratory compromise, respiratory insufficiency, septic shock and unexplained death). One patient who crossed over from placebo to cabozantinib had an unknown cause of death, and one patient died of intracerebral haemorrhage while receiving treatment with placebo.

Table 1
Overview of efficacy results.

	CRPC[a]	MEL[a]	OC[a,b]	NSCLC[a]	MBC[a,b]	HCC[a]	GC	SCLC	PAC
	(*N* = 171)	(*N* = 77)	(*N* = 70)	(*N* = 60)	(*N* = 45)	(*N* = 41)	(*N* = 21)	(*N* = 21)	(*N* = 20)
Lead-in stage									
Best overall response, n (%)									
Confirmed CR	0	0	1 (1.4)	0	0	0	0	0	0
Confirmed PR	8 (4.7)	4 (5.2)	14 (20.3)	6 (10.0)	6 (13.6)	2 (4.9)	1 (4.8)	1 (4.8)	0
SD	129 (75.4)	43 (55.8)	35 (50.7)	29 (48.3)	25 (56.8)	31 (75.6)	8 (38.0)	12 (57.1)	11 (55.0)
PD	19 (11.1)	19 (24.7)	9 (13.0)	12 (20.0)	9 (20.5)	3 (7.3)	10 (47.6)	7 (33.3)	5 (25.0)
Unable to evaluate	1 (0.6)	0	3 (4.3)	1 (1.7)	0	1 (2.4)	0	0	0
Missing	14 (8.2)	11 (14.3)	7 (10.1)	12 (20.0)	4 (9.1)	4 (9.8)	2 (9.5)	1 (4.8)	4 (20.0)
ORR (CR + PR), n (%)	8 (4.7)	4 (5.2)	15 (21.7)	6 (10.0)	6 (13.6)	2 (4.9)	1 (4.8)	1 (4.8)	0
95% CI	2.0, 8.7	1.8, 12.4	13.1, 32.4	4.4, 20.3	6.0, 25.7	0.9, 16.1	0.2, 21.8	0.2, 21.8	0%, 15.4
DCR (ORR + SD), n (%)[c]	112 (65.5)	33 (42.9)	35 (50.0)	23 (38.3)	21 (46.7)	27 (65.9)	7 (33.3)	9 (42.9)	7 (35.0)
95% CI	58.0, 72.3	32.0, 54.7	38.5, 61.5	26.1, 51.8	31.7, 61.6	50.0, 79.5	14.6, 55.1	21.8, 66.0	15.4, 58.9
Randomised stage									
Patients (cabo, pbo), n	31 (14, 17)	26 (13, 13)	13 (7, 6)	16 (8, 8)	10 (5, 5)	22 (10, 12)	5 (3, 2)	6 (4, 2)	6 (3, 3)
PFS cabo event count	9	7	5	4	3	9	1	3	2
Median PFS (95% CI), mo	5.5 (4.0, 8.5)	4.5 (1.8, 15.4)	4.9 (3.9, 13.6)	2.4 (1.4, 2.9)	6.9 (5.1, 13.5)	2.5 (1.3, 6.8)	UE (2.3, UE)	5.5 (1.9, 6.9)	2.8 (1.5, 2.8)
PFS pbo event count	11	11	4	6	5	9	2	2	1
Median PFS (95% CI), mo	1.4 (1.3, 2.7)	2.8 (1.5, 5.5)	1.4 (1.3, UE)	2.4 (1.4, 2.66)	1.1 (0.2, 1.4)	1.4 (1.3, 4.2)	1.0 (0.7, 1.34)	1.5 (0.9, 2.2)	0.7 (UE, UE)
HR (95% CI)	0.14 (0.04, 0.52)	0.47 (0.16, 1.35)	UE	0.94 (0.25, 3.54)	UE	0.82 (0.31, 2.12)	UE	0.24 (0.02, 2.67)	UE
Log-rank test *P* value	0.001	0.15	0.004	0.93	0.002	0.66	0.09	0.21	0.08
Overall study									
DOR, cabo patients, n	15	6	15	6	6	3	NA[d]	NA[d]	NA[d]
Median DOR (95% CI), mo	5.6 (4.3, 8.3)	5.6 (3.0, 13.9)	11.2 (7.2, UE)	6.9 (5.3, 10.7)	3.3 (2.8, 4.2)	4.2 (3.0, UE)	NA[d]	NA[d]	NA[d]
PFS from start of study, cabo patients, n	171	77	70	60	45	41	21	21	20
Median PFS[e], mo	6.8	2.8	5.5	4.0	5.2	4.3	1.4	3.4	2.7

CI, confidence interval; cabo, cabozantinib; CR, complete response; CRPC, castration-resistant prostate cancer; DCR, disease control rate; DOR, duration of objective response; GC, gastric/gastroesophageal junction adenocarcinoma; HCC, hepatocellular carcinoma; HR, hazard ratio; MBC, metastatic breast cancer; MEL, melanoma; NA, not applicable; NSCLC, non–small cell lung cancer; OC, ovarian cancer; ORR, objective response rate; PAC, pancreatic adenocarcinoma; pbo, placebo; PD, progressive disease; PFS, progression-free survival; PR, partial response; SCLC, small-cell lung cancer; SD, stable disease; UE, un-evaluable.

Best overall response was the proportion of patients treated in the lead-in stage with CR or PR through the week 12 tumour assessment; DCR was the proportion of patients treated in the lead-in stage with an overall response of CR, PR and SD at the week 12 tumour assessment.

[a] For patients who achieved the best response of a confirmed CR/PR, the first response date and confirmation date may occur at different study stages. Only first CR/PR occurrence is being summarised.

[b] For each cohort, one patient was excluded from the analysis during the lead-in stage due to lack of measurable disease at baseline.

[c] DCR determined at week 12.

[d] Median DOR was not determined for this cohort because of the low number of responses observed.

[e] Estimated using a piecewise method as previously described [6].

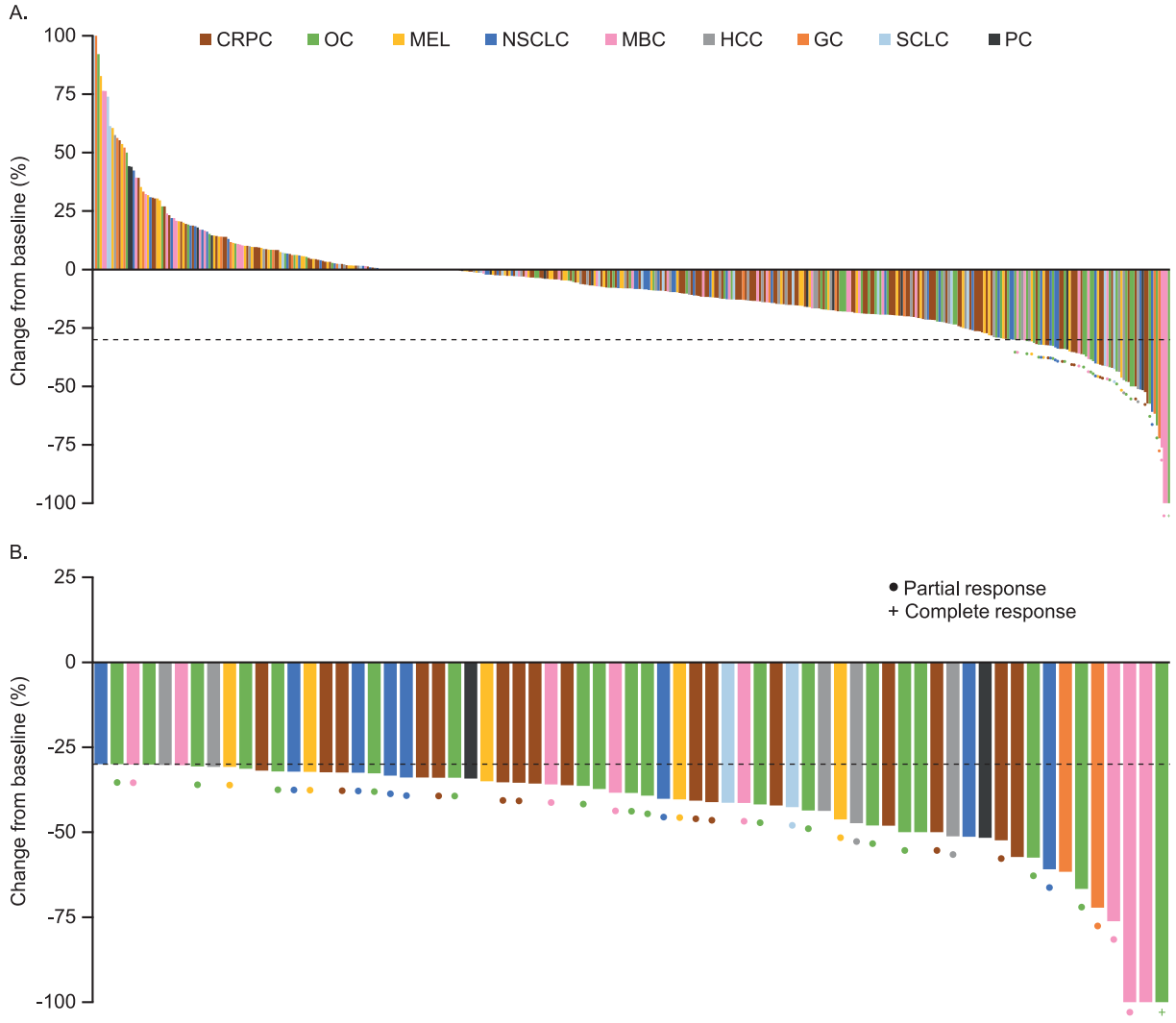

Fig. 2. **Best change of the sum of target lesions from baseline in all evaluable patients (A) and in evaluable patients who achieved ≥30% reduction (B)**. Note: 3 of 459 patients who were evaluable for objective response at week 12 were not evaluable for this analysis. CRPC, castration-resistant prostate cancer; GC, gastric/gastroesophageal junction adenocarcinoma; HCC, hepatocellular carcinoma; MBC, metastatic breast cancer; MEL, melanoma; NSCLC, non–small cell lung cancer; OC, ovarian cancer; PAC, pancreatic adenocarcinoma; SCLC, small-cell lung cancer.

4. Discussion

The goal of this RDT was to use the multi-tumour design as a screening tool to identify up to two tumour-specific cohorts that could be expanded to provide a sufficient number of patients with SD during the lead-in stage for generation of clinically meaningful PFS results during the randomised stage.

The study accrued within the estimated timelines. During the lead-in stage, cabozantinib demonstrated preliminary clinical activity in multiple tumour types. ORR ≥10% was observed in three tumour cohorts (OC, MBC and NSCLC), and DCR at week 12 ≥ 40% occurred in six tumour cohorts (HCC, CRPC, OC, MBC, NSCLC and MEL). Responses in patients treated with cabozantinib appeared to be durable and ranged from 3.3 months in MBC to 11.2 months in OC. In the three tumour cohorts with the highest numbers of patients in the randomised stage (CRPC, MEL and HCC), improved median PFS for cabozantinib treatment compared with placebo was observed. The analysis of overall PFS from the start of the study in the CRPC and HCC cohorts supported the PFS results obtained in the randomised stage.

The RDT design required periodic review of efficacy and safety across all tumour cohorts to adequately maintain enrolment within the scope of the study. Review of interim efficacy results led to the closure of the GC, SCLC and PAC cohorts after approximately 20 enrolled patients because these participants were deemed unlikely to benefit from cabozantinib. The other cohorts were allowed to continue with enrolment beyond 20

Table 2
Adverse events in ≥10% of patients (any grade) or ≥5% of patients (grade ≥III) irrespective of whether the event was considered by the investigator to be related to cabozantinib treatment ($N = 526$).

Preferred term	All, *n* (%)	Grade ≥III, *n* (%)
Patients with at least one event	524 (99.6)	392 (74.5)
Fatigue	345 (65.6)	65 (12.4)
Diarrhoea	317 (60.3)	55 (10.5)
Nausea	273 (51.9)	16 (3.0)
Decreased appetite	271 (51.5)	26 (4.9)
Vomiting	196 (37.3)	18 (3.4)
Palmar-plantar erythrodysesthesia syndrome	179 (34.0)	46 (8.7)
Constipation	171 (32.5)	11 (2.1)
Weight decreased	165 (31.4)	11 (2.1)
Dysgeusia	156 (29.7)	0
Dysphonia	142 (27.0)	0
Hypertension	127 (24.1)	55 (10.5)
Abdominal pain	126 (24.0)	29 (5.5)
Asthenia	118 (22.4)	32 (6.1)
Dyspnoea	109 (20.7)	21 (4.0)
Rash	102 (19.4)	5 (1.0)
Stomatitis	99 (18.8)	4 (0.8)
Aspartate aminotransferase increased	94 (17.9)	16 (3.0)
Pain in extremity	90 (17.1)	11 (2.1)
Cough	88 (16.7)	2 (0.4)
Dry mouth	87 (16.5)	0
Dizziness	87 (16.5)	4 (0.8)
Mucosal inflammation	84 (16.0)	4 (0.8)
Dehydration	84 (16.0)	29 (5.5)
Headache	80 (15.2)	4 (0.8)
Back pain	79 (15.0)	15 (2.9)
Oedema peripheral	78 (14.8)	4 (0.8)
Alanine aminotransferase increased	71 (13.5)	10 (1.9)
Hypomagnesaemia	70 (13.3)	2 (0.4)
Oral pain	68 (12.9)	2 (0.4)
Anaemia	66 (12.5)	21 (4.0)
Hypothyroidism	66 (12.5)	2 (0.4)
Dyspepsia	64 (12.2)	2 (0.4)
Hypokalemia	64 (12.2)	15 (2.9)
Urinary tract infection	64 (12.2)	7 (1.3)
Oropharyngeal pain	60 (11.4)	1 (0.2)
Thrombocytopaenia	58 (11.0)	11 (2.1)
Muscle spasms	56 (10.6)	0
Dry skin	54 (10.3)	0
Pulmonary embolism	29 (5.5)	29 (5.5)

patients. The highest enrolment was achieved in the CRPC cohort (N = 171). Suspension of the randomised stage was based on better than anticipated efficacy results (e.g. ORR in the OC cohort and high DCRs) as well as reports of symptomatic improvements (e.g. clinically relevant pain palliation in patients with CRPC with bone metastases), bone scan resolution and rapid clinical deterioration among patients randomised to placebo after achieving SD with cabozantinib during the lead-in stage (Supplementary Fig. S1). For these reasons, the RDT was converted to an open-label, non-randomised study with two expansion cohorts in CRPC and OC. Detailed results for the CRPC, MBC, MEL, HCC and OC cohorts as well as the CRPC non-randomised expansion cohort are reported separately [10–15].

The termination of the randomised stage of the study before achieving the maximum-allowed cohort enrolment limited the ability to draw definitive conclusions about PFS results. Nonetheless, the totality of the efficacy results throughout the study warranted further evaluation of cabozantinib activity in selected tumour types, including phase III studies in CRPC (ClinialTrials.gov, NCT01605227 [16] and NCT01522443) and an ongoing phase III study in HCC (NCT01908426).

The safety results with cabozantinib were consistent with those for patients with advanced cancer treated with VEGFR TKIs [17]. The observed AEs were similar to findings in other cabozantinib trials, and AEs were generally manageable with dose modifications and optimised supportive care.

In addition to the tumour types evaluated in this study, cabozantinib has been evaluated and granted regulatory approval for other oncology indications. Based on results from randomised phase III trials, cabozantinib tablets (60 mg) are approved for patients with advanced renal-cell carcinoma who have received prior anti-angiogenic therapy [18,19], and cabozantinib capsules (140 mg) are approved for patients with progressive, metastatic medullary thyroid cancer [20].

In summary, this phase II multi-cohort RDT allowed simultaneous evaluation of clinical activity and safety for cabozantinib in several tumour types. CRPC and OC were identified for further evaluation in open-label, non-randomised expansion cohorts, and the data collected for the CRPC and HCC cohorts supported the initiation of phase III programs in these indications.

Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.09.011.

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